Contents available at **PubMed**
www.aidsreviews.com

PERMANYER

AIDS Rev. 2016;18:81-8

Report from the International Conference on Viral Hepatitis (ICVH), San Francisco, March 2016

Vicente Soriano[1], Benjamin Young[2] and Norah Terrault[3]

[1]Infectious Diseases Unit, La Paz University Hospital, Madrid, Spain; [2]Internacional Association of Providers of AIDS Care, Washington, DC, USA; [3]Viral Hepatitis Center, Division of Gastroenterology, University of California at San Francisco, San Francisco, CA, USA

Abstract

The International Conference on Viral Hepatitis 2016 brought exciting news on the treatment of viral hepatitis. The conference was mainly focused on the most recent estimates of burden for HBV and HCV; the current gaps and prospects for regional and global HCV eradication; the use of HCV treatment as prevention; and the management of difficult-to-cure hepatitis C patients, including individuals who fail on direct-acting antivirals, people who inject drugs, and those with decompensated cirrhosis or renal insufficiency. Special patient populations, such as children, pregnant women, HIV-coinfected and persons with acute hepatitis C, were addressed separately. Data from both clinical trials and real-world experience were discussed. Further debates focused on hepatic conditions that may alter the management and outcome of viral hepatitis, such as fatty liver disease, liver transplantation, and hepatocellular carcinoma. **(AIDS Rev. 2016;18:81-8)**

Corresponding author: Vicente Soriano, vsoriano@dragonet.es

Key words

Hepatitis C. Hepatitis B. HIV. Sofosbuvir. Injection drug users. Coinfection. Cirrhosis. Liver transplantation.

Introduction

Liver and infectious diseases specialists from 22 countries convened in San Francisco on March 14-15, 2016 for a new edition of the International Conference on Viral Hepatitis (ICVH). The conference was co-sponsored by the International Association of Providers of AIDS Care (IAPAC), in partnership with the International Association for the Study of the Liver (IASL), and brought together a diverse panel of international experts who addressed the most relevant topics on viral hepatitis, with debates focused on new therapeutics and challenges for translating the good results of clinical trials into success across the steps of the medical care cascade.

Correspondence to:
Vicente Soriano
Servicio de Enfermedades Infecciosas
Hospital Universitario La Paz
Madrid, España
E-mail: vsoriano@dragonet.es

The burden of viral hepatitis

Up to 3.5 million people are chronically infected with HCV in the USA, and there are an estimated 100 million worldwide[1,2]. Globally, more than 700,000 HCV-infected people die each year from cirrhosis or primary liver cancer[1]. John Ward (Centers for Diseases Control and Prevention, Atlanta) remarked that new cases of HCV infection are also a concern in the USA, where acute HCV infection has increased by an alarming 150% in recent years, primarily fueled by increases in injection drug use among youth living in non-urban areas[3].

More than 200 million people (roughly 3% of the worldwide population) have chronic hepatitis B. Marion Peters (University of California, San Francisco) discussed

Note:
Slides and video presentations are available at:
http://www.iapac.org/icvh/icvh_conf_2016.html

the pros and cons of the current HBV armamentarium and treatment strategies[4] and the prospects of finding a "functional" cure, given that, in contrast to chronic HCV infection, so far there is no eradicative treatment for hepatitis B.

High direct-acting antiretroviral success but at high cost

Recent clinical trials have demonstrated that new, simple-to-use treatment regimens for persons living with HCV are safe and highly effective, leading to cure in the vast majority of treated patients. Nancy Reau (Rush University Medical Center, Chicago) and Anne Luetkemeyer (University of California, San Francisco) highlighted the effectiveness of currently approved regimens and the new pangenotypic combination of sofosbuvir and velpatasvir across distinct patient populations, including those who have failed prior therapies and those with decompensated cirrhosis[5-7].

Given the benefits of safe, convenient, and curative HCV therapy, why should we still be concerned about HCV? The answer is simple: patients do not benefit from drugs that they cannot afford[1]. Although CDC studies have shown that treating all people currently infected with HCV is cost-effective, the price of currently licensed medications, at $83,000-153,000 per course of treatment in the USA, is an insurmountable barrier for many health systems[1,8].

Despite US (AASLD) and European (EASL) guidelines recommending that all people currently infected with HCV should receive treatment[9,10], health plans and payers have responded to the high cost of HCV medications by instituting restrictive reimbursement policies. In most state Medicaid programs, only patients with advanced liver fibrosis qualify for new direct-acting antiretroviral (DAA) therapies. Drug expenditures for the treatment of HCV infection have declined as a result of mandated rebates for Medicaid and privately negotiated prices by health plans, but inequities in patient access to such therapies largely persist. Reductions in drug prices have already been set in many low-to-middle income countries. In the European Union, some countries (e.g. Spain) have recently acknowledged an agreement between government and pharmaceutical companies to set the weekly cost of DAA therapy at 1,000€. In this way, plans to treat patients with low stages of fibrosis (F0-F1) instead of only those with significant liver fibrosis (F2 or higher) can be anticipated.

The hepatitis C cascade

Beyond affordable drug pricing, the benefits of curative HCV therapy can be recognized only for persons who have been tested, know they are infected, and are linked to care. In the USA and the European Union, at least half of all people infected with HCV remain undiagnosed[1,10]. HCV testing in the USA is recommended for people born during 1945-1965 ("baby boomers"), a subgroup with a disproportionately high rate of chronic HCV infection. In addition, the US recommends HCV testing in certain risk groups, independent of birth year, including current or former ever users of injection drugs, all people living with HIV, children born to mothers with chronic HCV infection, and any patients with elevated alanine aminotransferase. People infected in the distant past are at highest risk of dying from HCV infection. In the USA, even a modest increase in implementation of the CDC recommendation for HCV testing could avert more than 320,000 deaths when that testing is linked to care and HCV curative treatment[1,9].

Edward Cachay (Owen Clinic, University of California, San Diego) highlighted that the HCV cascade care –the progressive steps needed to identify HCV-infected patients, provide them with care and treatment, and elicit cure– is lacking in most places[11]. A limiting factor with currently licensed therapies is the requirement that HCV persons undergo genotyping and hepatic fibrosis staging before the initiation of DAA therapy, complicating and delaying the treatment process. Most HCV people do not receive this level of care[12]. New pangenotypic regimens could simplify HCV management by reducing the need for genotyping, paving the way for simple "test and cure" strategies appropriate for primary care and other settings such as addiction treatment programs. The need for fibrosis staging to initiate therapy will also be eliminated by new DAA combinations that display equal efficacy across different liver fibrosis stages.

Kellyin Eagen (Department of Public Health, San Francisco) highlighted that educating providers about HCV testing, care, and treatment and creating innovative models for the delivery of DAA could dramatically decrease attrition across of the HCV cascade of care. As HCV regimens become simpler, DAA prescription would become more feasible for general practitioners, which would facilitate the patient's linkage to care and drug access[13]. Then, specialists would be required only for particularly difficult-to-manage individuals, such as those that already failed a first course of DAAs[14]. As a proof concept, in the ASCEND trial, 600 chronic hepatitis C patients were treated with sofosbuvir/ledipasvir in

Table 1.Predictors of direct-acting antiretroviral failure

Baseline	On-treatment
– Advanced cirrhosis	– Drug adherence
– Genotype 3 or 1a	– Side effects
– RAVs	– Drug interactions
– Prior interferon failure	
– Elevated serum HCV-RNA	
– IFNL4 unfavorable	
– African-American ethnicity	

RAVs: resistance-associated variants.

Table 2. Difficult-to-cure HCV populations

- End-stage renal disease
- Decompensated cirrhosis
- Prior DAA failures
- Potential drug interactions:
  - HIV, transplant recipients, psychiatric, elderly, etc.
- Difficult drug adherence:
  - Homeless, illegal immigrants, jail, active IDU, psychiatric
- Insufficient data:
  - Alcoholics, NASH-obese-diabetics, HBsAg+

DAA: direct acting antivirals; IDU: injection drug user; NASH: nonalcoholic steato-hepatitis.

Washington, DC, either by hepatitis specialists or general practitioners/nurses. Despite 96% of patients being African Americans, 25% HIV-coinfected, and 20% with cirrhosis, the sustained viral response (SVR) rates were above 92% and did not differ statistically between prescriber groups[15].

Direct-acting antiretroviral treatment failure

Current combinations of DAAs provide cure to most treated chronic hepatitis C patients. However, 5-15% of patients experience treatment failure in clinical trials and in preliminarily real-world studies. Failures are generally represented by individuals with more than one baseline predictor of lower response, such as advanced liver cirrhosis, infection with HCV genotypes 3 or 1a, elevated baseline serum HCV RNA, or prior interferon failure (Table 1). The presence of resistance-associated variants (RAV) at baseline may further compromise the efficacy of current regimens in this subset of patients, especially in cirrhotics or when treatment is given for short periods (less than 12 weeks).

Besides baseline predictors of poor response, there are particularly difficult-to-cure patient populations that require further consideration (Table 2). Kosh Agarwal (King's College Hospital, London) addressed the controversies surrounding DAA therapy in liver and renal transplant recipients, highlighting that the assessment of safety in patients with decompensated cirrhosis may be difficult, with unexpected toxicities, such as lactic acidosis, potentially attributable to the natural history of decompensated liver disease or drug toxicity[16,17].

Failure of DAA treatment is mostly the result of HCV relapse after completion of hepatitis C treatment. Rarely, viral breakthrough may occur during treatment. If so, the medication must be stopped as soon as possible since no benefit could be expected and RAVs may also have the opportunity to be fixed into the new emerging viral population through further accumulation of compensatory changes that enhance viral fitness of initial RAVs.

Since most current DAA regimens include an NS5A inhibitor and the corresponding RAVs selected in most patients failing treatment tend to persist thereafter, it seems worth performing HCV drug resistance testing for assisting the choice of the retreatment regimen. There is wide cross-resistance between distinct NS5A inhibitors and therefore the presence of RAVs to any agent within this drug class precludes full activity of other drugs in class. In contrast, RAVs to other DAAs tend to vanish over time (Fig. 1).

Table 3 records the major considerations for HCV retreatment, including how urgent is it and whether there is any chance to wait for better DAAs. Failure to achieve SVR with DAA regimens is commonly associated with the emergence of RAVs[18]. To avoid cross-resistance, recent guidelines recommend that patients who have failed on NS5A inhibitors should be retreated with sofosbuvir (NS5B inhibitor) combined with simeprevir (protease inhibitor); however, supporting evidence is scarce. In a real world study that evaluated 16 patients with HCV genotypes 1 or 4 infection and advanced fibrosis or cirrhosis who had failure of daclatasvir plus peginterferon/ribavirin, with or without asunaprevir (protease inhibitor), retreatment for 12 weeks with sofosbuvir plus simeprevir provided SVR to 14 patients[19]. The remaining two patients relapsed (both had HCV genotype 1a with cirrhosis). These findings support the concept of retreating NS5A inhibitor failures with sofosbuvir/simeprevir. However, more than 12 weeks of DAA treatment and/or

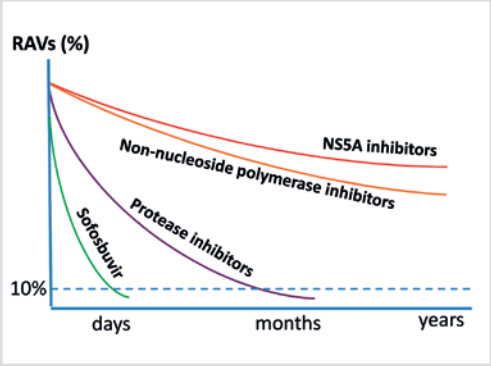

Figure 1. *Estimated clearance time for resistance-associated variants. RAVs: resistance-associated variants.*

Table 3. Considerations for HCV retreatment

How urgent is it? Any chance to wait for better direct-acting antiretrovirals?
– Virologic challenges: • Presence of RAVs (prior DAA failure) • Exclude HCV genotype shift (misinterpretation) • Exclude HCV re-infection (risk behaviors)
– Strategic management: • Adding ribavirin • Extent the length of therapy
– Maximize drug benefit: • Avoid drug interactions (co-morbidities) • Prevent and manage side effects • Ensure drug adherence

DAA: direct-acting antiretrovirals. RAVs: resistance-associated variants.

the addition of ribavirin should be considered to maximize the chances of SVR in this difficult-to-cure patient population[20].

With respect to HCV treatment failures using ombitasvir/paritaprevir/ritonavir with or without dasabuvir (3D), which often select for RAVs with reduced susceptibility to both protease and NS5A inhibitors, emerging data support that retreatment with triple combinations including other protease and NS5A inhibitors along with sofosbuvir given for 24 weeks and adding ribavirin allows to cure most patients. Alternatively, preliminary data suggest that new pangenotypic agents targeting the protease and NS5A (i.e. ABT-493 and ABT-530) with activity against RAVs may be an equally good option for individuals with multidrug resistance viruses.

Special populations for direct-acting antiretroviral therapy

Despite the 90-95% SVR rates in most DAA studies, distinct patient populations may have special management features, such as increased risk for drug-drug interactions (i.e. HIV or transplantation), more difficult social environment (i.e. prisoners, alcoholics, or injection drug users), comorbidities (i.e. renal impairment, non-alcoholic steatohepatitis, or HBV coinfection), or special periods in life (i.e. childhood or pregnancy)[21].

Children with either hepatitis B or C must be considered as a special population when considering treatment interventions. Kathleen Schwarz (Johns Hopkins Children's Center, Baltimore) highlighted that despite universal HBV vaccination in the USA since 1982, the prevalence of serum HBsAg+ is relatively high nationwide as result of children born or adopted from endemic regions in Asia. Accordingly, most harbor HBV genotype C. With respect to hepatitis C, the major problem is lack of diagnosis (< 5% in one US study). Therapeutic trials with DAAs are ongoing in children[22].

Tram Tran (Cedars-Sinai Medical Center, Los Angeles) addressed the management of hepatitis C in pregnant women, stressing that generally there is no urgency to treat HCV during gravidity, since there is no aggravation of liver disease with pregnancy and perinatal transmission is very low (3-10% in a recent meta-analysis), unless HIV coinfection is present and/or very high levels of viremia exist[22]. Furthermore, if children became infected with HCV, today's hopes for cure are very high. With respect to hepatitis B in pregnancy, Dr. Tran highlighted the benefit of HBV nucleos(t)ide therapy during the third trimester of gestation, reducing viremia and the chances of HBV exposure for the newborn[23].

Fatty liver disease is the next epidemic of cirrhosis, as was emphasized by Zobair Younossi (Inova Heath, Fairfax, VA), who took as example HIV disease to explain the dynamic nature of major liver conditions over time (Fig. 2)[24]. He highlighted that all patients that achieve hepatitis C cure should try to avoid obesity and the metabolic syndrome. If present, active measures should be undertaken, including diet, exercise, and therapeutic control of diabetes and dyslipidemia. Only in this way can reversion of HCV-related liver damage occur and provide clinical benefit.

HCV treatment as prevention

The benefits of HCV cure are not limited to the prevention and/or amelioration of liver disease complications and death in chronic carriers[25]. Benefits extend

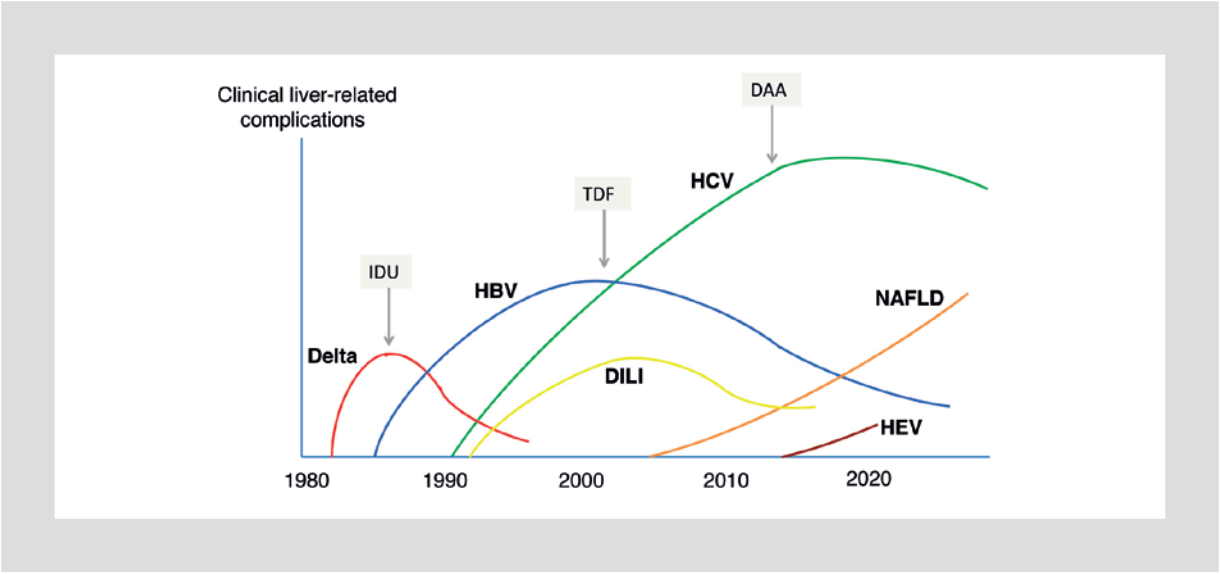

Figure 2. *Time trends in liver disease etiologies in HIV patients* (adapted with permission from Soriano, et al.)[24]. *DAA: direct-acting antiretrovirals; TDF: tenofovir disoproxil fumarate; IDU: injection drug user; NAFLD: nonalcoholic fatty liver disease; DILI: drug-induced liver injury.*

beyond the liver, improving extrahepatic complications such as diabetes and cardiovascular disease. Furthermore, HCV cure has major public health implications since viral eradication in carriers prevents viral transmission[26,27]. A case for prioritization of DAA therapy to prevent HCV outbreaks was discussed in three scenarios: patients on hemodialysis, men who have sex with men (MSM), and people who inject drugs (PWID).

Seng-Gee Lim (Yoo Loo Lin School of Medicine, Singapore University) reported a recent major outbreak of hepatitis C among patients on hemodialysis in Singapore. A total of 25 patients were involved, of whom 22 had renal transplants. There were eight deaths. The presence of very high serum HCV RNA contributed to the elevated contagion rate, although sterile procedures were violated occasionally. Dr. Lim also addressed major issues of hepatitis C spreading and treatment in Asia, where prevalence ranges from 0.5% to as high as 4.7%. The wide distribution of HCV genotypes increases the complexity of HCV treatment across Asia, with a dominance of genotype 1b in the East, genotype 3 in the South/Southeast, and genotype 6 in Indochina. Approvals for the new oral DAAs in Asia have been very slow, and consequently, peginterferon and ribavirin are still widely used. Nonetheless, as in the USA, the main issues in Asia are related to the initial steps in the HCV cascade of care, namely HCV screening and linkage to care.

Daniel Fierer (Icahn School of Medicine at Mount Sinai, New York) stressed the ongoing epidemics of acute hepatitis C among MSM, mostly in people who were also HIV infected, and the potential benefit of early treatment interventions for halting HCV spreading[28-30]. Up to a quarter of newly infected HCV individuals may clear HCV spontaneously, but 75% will progress to chronic infection. While treatment to prevent HCV transmission must be advocated, equally important are education and other prevention strategies to reduce the risk of many other sexually transmitted diseases in MSM.

Diana Sylvestre (Oasis Clinic, Oakland, CA) addressed the management of hepatitis C in PWID. She highlighted that a large proportion of HCV infections in the developed world occurs in PWID. Treatment uptake is low despite the rising burden of HCV-related liver disease among PWID. Multiple barriers preclude the optimal care of hepatitis C in PWID[29], including concerns on poor medication adherence[31], HCV reinfection[32], and the potential risk for selection and transmission of DAA-resistant viruses[33].

The controversy about whether or not to treat hepatitis C in active intravenous drug users will be cooled as the more effective and easy to take new DAA are becoming available[34]. With these medications, the future for PWID with hepatitis C is very promising, even for the large group of them coinfected with HIV[35]. In the best scenario, HCV eradication from infected PWID will provide a unique opportunity for testing the success of "treatment as prevention", as eliminating HCV from the large pool of PWID will certainly reduce the risk of acquisition by uninfected persons with high-risk behaviors.

Hepatitis C therapy in people who inject drugs

HCV infection is mainly transmitted parenterally, as unsafe medical procedures are the leading route of HCV transmission worldwide[27]. However, a large proportion of prevalent cases and the majority of new HCV infections occur among PWID. In 2013 a panel of experts signed a document discussing how hepatitis C should be managed in PWID[36]. Their major argument was that despite the large number of PWID with hepatitis C worldwide and the high efficacy of new HCV therapies, only a small fraction of them have been treated. Given that many PWID were infected decades ago, the proportion with advanced liver disease is rising, thus increasing the urgency of identifying the potential obstacles to HCV treatment and ways to overcome them.

Christian Ramers (Family Health Centers, San Diego, CA) highlighted that prescribing hepatitis C treatment in PWID has so far often been discouraged due to concerns of medication adherence, management of adverse events, and HCV reinfections. However, when comprehensive support is given, treatment response rates in PWID resemble those obtained in other hepatitis C patients[37]. Multidisciplinary teams including social workers, experts in substance abuse, and psychiatrists, along with infectious disease experts and/or gastroenterologists, should work together to maximize treatment success in PWID with hepatitis C. However, these resources are generally not available in most developing regions where injection drug use is currently spreading (in parallel with hepatitis C), such as in several Eastern European countries and Russia, Southeast Asia, and some Latin American urban populations[14]. Moreover, reaching active injectors and enrolling them into medical care is an important obstacle itself.

There is little doubt that delivering hepatitis C treatment to PWID is mainly problematic in active injectors. In contrast, HCV treatment in former addicts on opioid substitution programs (i.e. methadone or buprenorphine) can be addressed without much controversy. Clearly, the commitment to provide medical care to active injecting drug users needs to prioritize aspects other than hepatitis C. Complications of their lifestyle, including both social (i.e. crime, unstable housing) and medical conditions (i.e. endocarditis, overdose) may occasionally be life threatening and thus addressed first[38]. A comprehensive approach to care must be undertaken, but with attention to HCV cure included in the overall efforts to recover from their injection drug use lifestyle.

While the major challenge of treating hepatitis C in active injection drug users is poor medication adherence, the results of treatment in PWID on opioid substitution programs (with either methadone or buprenorphine) are similar or often better than in any other group, possibly due to more frequent infection with HCV genotype 3, younger age, and mild liver fibrosis[39].

Although enthusiasm is unabated, it is worth keeping in mind that the expected high cost of these new HCV medications will preclude their rapid availability everywhere and for everyone. Thus, education, social support, psychiatric care, and comprehensive harm-reduction programs, including provision of clean drug injection equipment and especially recruitment in opioid substitution clinics, should remain a priority in PWID. Additionally, hepatitis C is only one of the multiple potential life-threatening complications in PWID. While individual freedom must be respected, there is value in developing comprehensive approaches to discourage injection drug use, given its tremendously harmful effects on persons and society[38]. Something similar has been done with tobacco smoking and it has been a success.

Is HIV still a special patient population?

HCV affects a greater proportion of persons living with HIV (PLHIV) than the general population[35]. This is due to shared risk factors for transmission, mainly percutaneous exposure to blood or blood products contaminated with HCV and/or sexual transmission (particularly among HIV-positive MSM)[28-30]. Roughly 4.5 million PLHIV worldwide are coinfected with HCV[35]. Until recently, HIV/HCV-coinfected individuals had been considered a special population because they progressed faster to cirrhosis and responded less well to interferon-based therapies than HCV-monoinfected persons[11,40]. Interferon relies on activating the individual's immune response to clear HCV, and immunity is already impaired in PLHIV. Since less than 5% of HIV-infected individuals with known HCV infection were treated in the interferon era[11,41], it is not surprising that HCV has become the leading cause of liver-related mortality among PLHIV otherwise well controlled on antiretroviral therapy[42].

In the new DAA era, clinical trials have consistently demonstrated that PLHIV can achieve SVR rates in excess of 90%, similar to patients without HIV coinfection[43]. Although management of drug-drug interactions (DDI) between DAA and antiretroviral medications remains an important caveat, several online resources help to manage DDI and ease the clinicians' work when considering HCV treatment in this population.

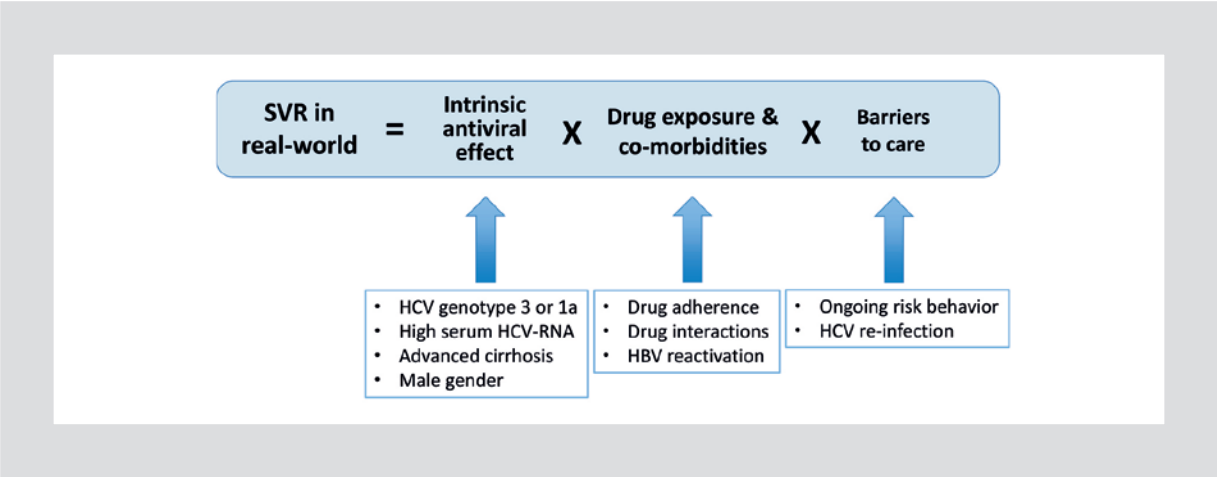

Figure 3. *The equation for hepatitis C therapy success* (adapted with permission from Cachay, et al).[44]. *SVR: sustained virological response.*

Does this mean that we need to stop considering PLHIV coinfected with HCV as a special population for the treatment of hepatitis C? Maurizio Bonacini (Sutter Health, San Francisco) said that the answer is, No.

Considering that SVR rates in HCV clinical trials offer the potential of curing most PLHIV coinfected with HCV, the translation to real-life scenarios must be interpreted cautiously. In this regard, SVR could be viewed as the net result of an equation that depends on three key clinical variables: (i) the intrinsic antiviral effect, (ii) drug exposure and concurrent comorbidities, and (iii) ongoing barriers to care (Fig. 3)[44]. In most clinical trials, SVR rates are the direct reflection of potent DAA efficacy because other factors of the equation were study exclusion criteria and therefore did not impact on SVR. In other words, a selection bias of PLHIV was made in most HCV registration trials to demonstrate that HIV was not a negative predictor of DAA response[45].

In real life, most PLHIV coinfected with HCV in Western countries have a long HIV medication history and frequent comorbid conditions. Emerging data from real-world HIV/HCV cohorts demonstrate that antiretroviral changes prior to HCV therapy are common, including more than 40% of PLHIV who initiated HCV therapy in San Diego[45]. Moreover, up to 30% of them were antiretroviral-experienced patients with prior HIV drug resistance, further complicating drug choices and avoidance of harmful DDI. Concerns on drug interactions and polypharmacy increase due to the higher rate of concurrent comorbidities in PLHIV compared to the general population. The presence of these conditions not only increase the number of medications and the potential risk for DDI, but also could restrict DAA options in PLHIV due to additional concerns, such as recently highlighted use of sofosbuvir along with amiodarone[46-48]. On the other hand, the higher rate of hepatitis B or hepatitis delta in PLHIV might account for more frequent HBV reactivation episodes and force premature DAA discontinuation[49].

The PLHIV coinfected with HCV have a high prevalence of ongoing barriers to care, such as active drug/alcohol use, neuropsychiatric disease, and/or unstable housing. In fact, the presence of ongoing barriers to care was the main reason for not initiating HCV therapy in PLHIV in the interferon era[11,41]. From a practical point of view, successful HCV treatment of patients with ongoing barriers to care can be accomplished, but requires a dedicated multidisciplinary team to support them[31,38]. In particular, monitoring DAA adherence and minimizing risk behaviors are the most crucial. The most worrisome scenario would be represented by poor DAA adherence along with ongoing risk behaviors, such as active injection drug use and/or persistent high-risk sexual practices, with an increased likelihood of HCV reinfection[32], or treatment failure and selection and transmission of RAVs[33]. In this regard, periodic surveillance of DAA resistance is advisable in these populations, especially to NS5A inhibitors for which RAVs do not vanish and persist over time, compromising most current DAA combinations[20].

A recent real-world study that examined the treatment of 363 chronic hepatitis C patients found that HIV was an independent predictor for lack of HCV treatment response[50]. Whether this observation was due to individual factors (i.e. greater viral load, more frequent genotype 3, cirrhosis, etc.)[51,52] or the cumulative/synergistic effect of several of the aforementioned factors remains unclear.

Nowadays using DAA we can cure HCV in most PLHIV. Although PLHIV will respond equally as well as the general population in terms of HCV antiviral efficacy, special attention is worthwhile to avoid DDI, manage comorbidities, and address ongoing barriers to care. Only with a deeper understanding of the issues surrounding what makes PLHIV coinfected with HCV a special population can we unite efforts to scale-up DAA therapy in an era where HCV could be a potentially eradicable disease, even across different geographical areas and healthcare systems.

References

1. Ward J, Mermin J. Simple, effective, but out of reach? Public health implications of HCV drugs. N Engl J Med. 2015;373:2678-80.
2. Gower E, Estes C, Blach S, et al. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol. 2014;61:45-57.
3. Suryaprasad A, White J, Xu F, et al. Emerging epidemic of HCV infections among young non-urban persons who inject drugs in the United States, 2006-2012. Clin Infect Dis. 2014;59:1411-9.
4. Martin P, Lau D, Nguyen M, et al. A treatment algorithm for the management of chronic HBV infection in the United States: 2015 update. Clin Gastroenterol Hepatol. 2015;13:2071-87.
5. Feld J, Jacobson I, Hezode C, et al. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5 and 6 infection. N Engl J Med. 2015;373:2599-607.
6. Foster G, Afdhal N, Roberts S, et al. Sofosbuvir and velpatasvir for HCV genotypes 2 and 3. N Engl J Med. 2015;373:2608-17.
7. Curry M, O'Leary J, Bzowej N, et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. N Engl J Med. 2015; 373:2618-28.
8. Chahal H, Marseille E, Tice J, et al. Cost-effectiveness of early treatment of HCV genotype 1 by stage of liver fibrosis in a US treatment-naive population. JAMA Intern Med. 2016;176:65-73.
9. AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD/IDSA. Recommendations for testing, managing and treating adults infected with HCV. Hepatology. 2015;62:932-54.
10. European Association for Study of Liver. EASL Recommendations on Treatment of Hepatitis C 2015. J Hepatol. 2015;63:199-236.
11. Cachay E, Hill L, Wyles D, et al. The hepatitis C cascade of care among HIV-infected patients: a call to address ongoing barriers to care. PLoS One. 2014;9:e102883.
12. Cachay E, Wyles D, Hill L, et al. The impact of direct-acting antivirals in the hepatitis C-sustained viral response in HIV-infected patients with ongoing barriers to care. Open Forum Infect Dis. 2015 2:ofv168.
13. Arora S, Thornton K, Murata G, et al. Outcomes of treatment for hepatitis C virus infection by primary care providers. N Engl J Med. 2011;364:2199-207.
14. Zoulim F, Liang T, Gerbes A, et al. Hepatitis C virus treatment in the real world: optimising treatment and access to therapies. Gut. 2015;64:1824-33.
15. Kattakuzhy S, Gross C, Teferi G, et al. High efficacy of HCV treatment by primary care providers: the ASCEND study. CROI 2016. Boston, Feb 22-25, 2016 [Abstract 538LB].
16. Welker M-W, Luhne S, Lange C, et al. Lactic acidosis in patients with hepatitis C virus related cirrhosis and combined ribavirin/sofosbuvir treatment. J Hepatol. 2016;64:790-9.
17. Hoofnagle J. Hepatic decompensation during direct-acting antiviral therapy of chronic hepatitis C. J Hepatol. 2016;64:763-5.
18. Reau N, Fried M, Nelson D, et al. HCV council – critical appraisal of data: recommendations for clinical practice in a rapidly evolving therapeutic landscape. Liver Int. 2016;36:488-502.
19. Hézode C, Chevaliez S, Scoazec G, et al. Retreatment with sofosbuvir and simeprevir of patients with HCV GT1 or 4 who previously failed a daclatasvir-containing regimen. Hepatology. 2016 [Epub ahead of print].
20. Benitez-Gutierrez L, Barreiro P, Labarga P, et al. Prevention and management of treatment failure to new oral hepatitis C drugs. Exp Opin Pharmacother. [In press].
21. Soriano V, Labarga P, de Mendoza C, et al. New hepatitis C therapies for special patient populations. Expert Opin Pharmacother. 2016;17:217-29.
22. Karnsakul W, Alford M, Schwarz K. Managing pediatric hepatitis C: current and emerging treatment options. Ther Clin Risk Manag. 2009;5: 651-60.
23. Patton H, Tran T. Management of hepatitis B during pregnancy. Nat Rev Gastroenterol Hepatol. 2014;11:402-9.
24. Soriano V, Barreiro P, Sherman K. The changing epidemiology of liver disease in HIV patients. AIDS Rev. 2013;15:25-31.
25. Soriano V, Labarga P, Fernandez-Montero JV, et al. Hepatitis C cure with antiviral therapy - benefits beyond the liver. Antivir Ther. 2016;21:1-8.
26. Martin N, Thrnton A, Hickman M, et al. Can HCV DAA treatment as prevention reverse the HCV epidemic among MSM in the UK? Epidemiological and modeling insights. Clin Infect Dis. 2016;62:1072-80.
27. Thomas D. Global control of hepatitis C: where challenge meets opportunity. Nat Med. 2013;19:850-8.
28. Kaplan-Lewis E, Fierer D. Acute HCV in HIV-infected MSM: modes of acquisition, liver fibrosis, and treatment. Curr HIV/AIDS Rep. 2015;12: 317-25.
29. Boesecke C, Grint D, Soriano V, et al. EuroSIDA in EuroCoord. Hepatitis C seroconversions in HIV infection across Europe: which regions and patient groups are affected? Liver Int. 2015;35:2384-91.
30. Van der Laar T, Matthews G, Prins M, Danta M. Acute hepatitis C in HIV-infected men who have sex with men: an emerging sexually transmitted infection. AIDS. 2010;24:1799-812.
31. Altice F, Kamarulzaman A, Soriano V, Schechter M, Friedland G. Treatment of medical, psychiatric, and substance use comorbidities in people infected with HIV who use drugs. Lancet. 2010;376:367-87.
32. Midgard H, Bjoro B, Maeland A, et al. Hepatitis C reinfection after sustained virological response. J Hepatol. 2016;64:1020-6.
33. Franco S, Tural C, Nevot M, et al. Detection of a sexually transmitted HCV protease inhibitor-resistance variant in a HIV-infected homosexual man. Gastroenterology. 2014;147:599-601.
34. Soriano V, Labarga P, Fernández-Montero JV, et al. The changing face of hepatitis C in the new era of direct-acting antivirals. Antivir Res. 2013;97:36-40.
35. Platt L, Easterbrook P, Gower E, et al. Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. Lancet Infect Dis. [Epub ahead of print].
36. Robaeys G, Grebely J, Mauss S, et al. Recommendations for the management of hepatitis C virus infection among people who inject drugs. Clin Infect Dis. 2013;57(Suppl 2):129-37.
37. Hellard M, Sacks-Davis R, Gold J. Hepatitis C treatment for injection drug users: a review of the available evidence. Clin Infect Dis. 2009;49:561-73.
38. Soriano V, Gallego L. Treating hepatitis C in injection drug users. Nat Rev Gastroenterol Hepatol. 2013;10:568-9.
39. Melin P, Chousterman M, Fontanges T, et al. Effectiveness of chronic hepatitis C treatment in drug users in routine clinical practice: results of a prospective cohort study. Eur J Gastroenterol Hepatol. 2010;22: 1050-7.
40. Konerman M, Mehta S, Sutcliffe C, et al. Fibrosis progression in HIV/hepatitis C virus coinfected adults: prospective analysis of 435 liver biopsy pairs. Hepatology. 2014;59:767-75.
41. Grint D, Peters L, Schwarze-Zander C, et al. Temporal changes and regional differences in treatment uptake of hepatitis C therapy in EuroSIDA. HIV Med. 2013;14:614-23.
42. Data Collection on Adverse Events of Anti-HIV Drugs Study Group; Smith C, Sabin C, Lundgren J, et al. Factors associated with specific causes of death amongst HIV-positive individuals in the D:A:D study. AIDS. 2010;24:1537-48.
43. Saeed S, Strumpf E, Walmsley S, et al. How generalizable are the results from trials of direct-antiviral agents to people coinfected with HIV/HCV in the real world? Clin Infect Dis. 2016;62:919-26.
44. Cachay E, Soriano V. Is HIV still a special population for the treatment of hepatitis C? AIDS. [In press].
45. Cachay E, Ballard C, Colwell B, Torriani F. Real-world effectiveness of direct-acting antivirals for hepatitis C among HIV-infected patients with genotype 1. 5th International Conference on Viral Hepatitis (ICVH 2016). San Francisco, CA. March 14-15 [Oral Abstract 036].
46. Renet S, Chaumais MC, Antonini T, et al. Extreme bradycardia after first doses of sofosbuvir and daclatasvir in patients receiving amiodarone: 2 cases including a rechallenge. Gastroenterology. 2015;149:1378-80.
47. Back D, Burger D. Interaction between amiodarone and sofosbuvir-based treatment for hepatitis C virus infection: potential mechanisms and lessons to be learned. Gastroenterology. 2015;149:1315-7.
48. Fontaine H, Lazarus A, Pecriaux C, et al. Bradyarrhytmias associated with sofosbuvir treatment. N Engl J Med. 2015;373:1886-8.
49. De Monte A, Courjon J, Anty R, et al. Direct-acting antiviral treatment with HCV: reactivation of hepatitis B virus coinfection as a further challenge. J Clin Virol. 2016;78:27-30.
50. Arias A, Aguilera A, Soriano V, et al. Rate and predictors of treatment failure to all-oral HCV regimens outside clinical trials. Antivir Ther. [In press].
51. Barreiro P, Labarga P, de Mendoza C, et al. High serum HCV-RNA in chronic hepatitis C patients coinfected with HIV despite successful antiretroviral therapy. Antivir Ther. [Epub ahead of print].
52. Chen T, Terrault N. Treatment of chronic hepatitis C in patients with cirrhosis. Curr Opin Gastroenterol. 2016;32:143-51.